DIABETES MELLITUS: NEW DEVELOPMENTS AND THEIR IMPLICATION FOR A PREVENTION STRATEGY

• The classification of type I and type II diabetes mellitus has been made under the guidance of the World Health Organization (WHO) (see WHO report, 1980, and Ref.1).

Type I or insulin dependent diabetes mellitus (IDDM) is characterized by absolute insulin deficiency due to an autoimmune destructive process of the β-cell in the islets of Langerhans. The main clinical symptoms for IDDM are thirst, polyuria and acidosis. Antibodies to islets cells are found, while indications of residual insulin production (the so-called C-peptide levels) appear at low levels at the onset of the disease. Type I diabetes can develop at any age (often below 30 years old). Genetic factors seem to predispose for the susceptibility to develop the autoimmune insulinitis by viral or other toxic causes (2,3).

GENETIC FACTORS

• The predisposition to type I diabetes mellitus is a complex multigene phenomenon. No single locus has been unequivocally demonstrated to be directly related to the disease. Although certain alleles of HLA loci, e.g. the HLA-DQ, are candidates, their effects are seemingly not related to presentation of the autoantigenic peptide to self-reactive T cells. Their function in shaping the T cell repertoire remains to be studied (2-4). In the DQB genes, especially the amino acid at position 57 (Asp57), seems to be directly correlated with resistance.

A better understanding of the genetics and pathogenesis of type I diabetes can be obtained by analysis of HLA-haplotypes. Extended haplotype, stretches of chromosomes conserved in evolution may contain the key to unravel the mechanism of genetic predispositions to type I diabetes (4).

Immunointervention therapy in type I diabetes can be applied as long as p-cell destruction is incomplete and p-cell function can be preserved. “The most elegant approach of specific intervention in the p-cell destruction process would only affect the component of the immune system involved in this disease process” (4). At least two autoimmune targets on pancreatic p-cells have been determined (GAD and p38) to which this
specific immunotherapy could be directed too.

The genetic defects in type II diabetes are approached in a different way. Since insulin is still present in the early phase of disease, the attention is more directed towards the genes producing proteins involved in the signal transduction (Fig. 1). Mutations have been published for insulin receptor genes, insulin receptor substrate-1 (IRS-1) genes, glucose transporter 4 (GLUT4), and phosphatidylinositol 3-kinase (PI-kinase). On the genes of enzymes involved in phosphorylation and in glycogen synthesis no mutations are published. Some mutations are found outside the signaling pathway. They concern the glucagon receptor gene and the β3-adrenergic receptor gene.

A new subtype of diabetes was described at the end of the eighties, maternally inherited diabetes and deafness (MIDD). This type of diabetes is characterized by maternal inheritance and a hearing disturbance. The maternal inheritance focussed research on gene mutations to mitochondrial DNA. A mutation was found in the position 3234 of mitochondrial DNA coding for a tRNA<sup>Leu</sup> (UUR). A number of proteins involved in the respiratory chain complexes are disturbed due to impaired leucine incorporation (5).

**ENVIRONMENTAL FACTORS**

A higher prevalence rate for type II diabetes is noted for low-birth-weight subjects aged 50 to 70 years. Presumably the association between type II diabetes and low weight at birth is not related to a coincidence of type II diabetes genotype and a genetically determined low birth weight (6). In this respect, intrauterine malnutrition, especially protein deficiency, is an important factor. Switching from a rural to an urban lifestyle increases type II diabetes. The *thrifty gene hypothesis* says that "for societies living in environments with unstable food supplies, maximizing storage of surplus energy would enhance the probability of survival under periods of energy deficiency.

**Figure 1.** Schematic outline of insulin-induced glucose transport and glycogen synthesis. p85 and p110, subunits of PI-kinase; HK - hexokinase; ins - insulin; PTyr - phosphotyrosine; IRS1 - insulin receptor substrate 1; exo - exocytosis; endo - endocytosis; GLUT - glucose transporter. Courtesy of Maassen (9)
The abundance of food typical for modern Westernized society might lead to marked obesity and glucose intolerance in such a genotype (6). The expression of a diabetic genetic effect may also depend on the presence of obesity or reduced physical activity in the affected individual.

PREVENTION OF DIABETES MELLITUS

A major contribution to improved health status will be provided by prevention or delay of diabetes (7). Three main types of prevention of diabetes can be distinguished (see WHO report, 1994): (i) primary prevention is related to the genetic changes seen in diabetes, (ii) secondary prevention is related to the metabolic changes noted in diabetes, and (Hi) tertiary prevention concerns the development of secondary complications.

To prevent diabetes mellitus the cause of disease must be known and treatment must be available. Both conditions cannot be met in diabetes. Therefore, prevention of diabetes can only be presented as general prevention. However, general information directed to and education of persons identified as high risk to develop diabetes mellitus can be more effective.

LESSONS FOR BULGARIA

What does this special volume of the Biomedical Reviews mean for the prevention and study of diabetes mellitus in Bulgaria?

Two important recommendations can be made:

(i) A public relations campaign has to start on radio and TV that indicates the risk factors involved in diabetes mellitus as outlined in the WHO report (1994) supported by the now free-obtainable insulin and other materials in Bulgaria.

- General preventive measurements have to be brought at the attention of the Bulgarian population. These are:
  (a) increase of physical activity, (b) right choices of food and beverages, and (c) reduction of overweight

- A special subcampaign has to be directed to persons identified as a high risk to develop diabetes mellitus.

- Extratraining programmes have to be developed for physicians in certain regions in Bulgaria (see Koeva and Koev [8] in this volume of Biomedical Reviews).

(ii) One or more scientific group(s) in Bulgaria studying diabetes mellitus has (have) to be developed by or related to a Diabetes Health Care Center. As can be learned from the history of polio in the Netherlands where one scientific group working on polio was extremely well involved in the polio research of the USA. The former developed inactivation and isolation of polio virus in the USA. This could be immediately applied in a vaccination prog-

(*; rume in the Netherlands, protecting several year groups .••> of Dutch children a head of the same year groups in Belgium. Compared to Belgium, billions of Dutch guilders of health care costs were saved. A National Institute for Diabetes must be the place to stimulate the knowledge and the care for diabetes as the Saint-Vincent Declaration asks that they must be developed in every country.

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